HEMODYNAMIC ALTERATIONS IN HYPERTENSIVE PATIENTS DUE TO CHLOROTHIAZIDE*

EDWARD D. FROHLICH, M.D.,† HAROLD W. SCHNAPER, M.D.,‡ ILSE M. WILSON, M.D.,† AND EDWARD D. FREIS, M.D.§

WASHINGTON, D. C.

ONLY two studies have been published that detail the changes in cardiac output after chlorothiazide.[1,2] Other reports[3,4] have alluded to the changes in cardiac output without tabulating any data. In the studies in which results were reported in detail, cardiac output was performed by the dye-dilution technic. Aleksandrow and his co-workers[1] reported variable results in 7 hypertensive patients whereas Dustan and her associates[2] demonstrated a consistent decrease. This communication reports on a series of hypertensive patients in whom cardiac output was measured before and after administration of chlorothiazide. In the majority of patients the direct Fick method was used, the dye-dilution technic being employed in the others.

MATERIAL AND METHODS

Seven male patients with moderately severe hypertension were selected for study. The average age was forty-eight years. None had a history of congestive heart failure. Before the control determinations were obtained, the patients were in the hospital, without antihypertensive medications, for three or more days depending on the time required for the blood pressure to reach a relatively constant level. All patients were given the usual hospital diet containing between 6 and 8 gm. of sodium chloride per day.

Experiments were carried out, with the patient fasting, approximately one hour after the oral administration of 100 mg. of pentobarbital. In the first 5 patients (Table 1), three control determinations of cardiac output were performed at fifteen-minute intervals by means of the direct Fick method. The catheter tip was placed in the mid-position of the right atrium to avoid the unnecessary risk of ventricular catheterization. In the last 2 patients (Table 1), cardiac outputs were determined with the use of the dye-dilution technic (T-1824). The dye was injected through a polyethylene catheter threaded into the axillary vein, and collections were made at two-second intervals from the femoral artery. After the first determination of cardiac output each subject was given 1.5 gm. of chlorothiazide daily for three days. *On the fourth day the cardiac output* was repeated. Blood and plasma volumes and hematocrit were determined from dye samples at ten, fifteen and twenty minutes. Blood and plasma volumes were determined in the first 5 patients (Table 1) by means of I^{131}-labeled albumin. Blood samples were obtained ten minutes after injection and were counted for gamma activity in a well counter.

Body weights were determined with the use of a beam-balance scale just before each determination of cardiac output. Calculations of the hemodynamic data in the patients studied by the direct Fick and dye-dilution technics were carried out according to the methods previously described.[5,6]

RESULTS

The cardiac output fell in 6 of the 7 patients after chlorothiazide. In Case 5 there was a 5 per cent increase in cardiac output. The average decrease in cardiac output for the entire group was 29 per cent. In the 6 subjects in whom the cardiac output fell, the decrease ranged from 8 to 50 per cent (average fall, 34 per cent).

The systolic pressure fell in all 7 patients. The decrease in systolic pressure ranged from 3 to 33 per cent, with a mean fall of 17 per cent. The diastolic pressure fell in only 5 of the 7 patients. In Case 5 there was a 5 per cent rise in diastolic pressure; there was no change in Case 7. The decreases in diastolic pressure ranged from 5 to 33 per cent. The average change for all patients was a decrease of 13 per cent. The mean arterial pressure fell in 6 of the 7 patients. In Case 5 there was a 2 per cent rise. The average fall was 15 per cent.

In the 3 patients in whom pressures in the right atrium were recorded, the following results were ob-

*From the Medical Service, Veterans Administration Hospital, and the Department of Medicine, Cardiovascular Research Laboratory, Georgetown University School of Medicine.

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†Fellow in cardiovascular research, Department of Medicine, Georgetown University School of Medicine.

‡Assistant professor of medicine, Georgetown University School of Medicine; assistant chief of medicine, Mount Alto Veterans Administration Hospital.

§Associate professor of medicine, Georgetown University School of Medicine; Senior Medical Investigator, Mount Alto Veterans Administration Hospital.

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tained after administration of chlorothiazide: a decrease of 5.5 mm. of mercury in Case 1; a decrease of 2.0 mm. in Case 2; and a decrease of 8.2 mm. in Case 4.

The plasma and blood volumes were decreased in 6 of the 7 patients studied. In Case 4 there was a 7 per cent increase in the plasma and blood volumes respectively. The mean decrease in the plasma volume for the entire group of 7 cases was 13 per cent. The hematocrit demonstrated a slight increase. The average weight loss was 3.2 kg.

The total peripheral resistance increased in 5 of the 7 patients. The increase averaged 33 per cent. In 2 patients there was a decrease in the total peripheral resistance of 2 and 23 per cent respectively.

TABLE 1. *Hemodynamics of Chlorothiazide in Hypertensive Patients.*

CASE NO.	AGE	CARDIAC OUTPUT		SYSTOLIC PRESSURE		DIASTOLIC PRESSURE		MEAN ARTERIAL PRESSURE	
		CONTROL	EXPERIMENTAL*	CONTROL	EXPERIMENTAL*	CONTROL	EXPERIMENTAL*	CONTROL	EXPERIMENTAL*
	yr.	*ml./min.*	*ml./min.*	*mm. Hg.*	*mm. Hg.*	*mm. Hg.*	*mm. Hg.*	*mm. Hg.*	*mm. Hg.*
1†	52	6112	2825	194	174	108	98	137	123
2†	52	5018	3649	314	209	156	119	209	149
3†	36	6481	5974	180	140	135	90	150	107
4†	45	4133	2085	223	176	141	134	168	148
5†	52	5281	5535	181	175	93	98	122	124
6	50	6336	3429	170	140	110	90	130	107
7	51	6286	4600	190	185	105	105	133	132
Averages	48	5664	4014	207	171	121	105	150	127
Mean percentage change		−29		−17		−13		−15	

*Results after 3 days of chlorothiazide therapy.
†Control value average of 3 separate determinations.

The plasma and blood volumes were decreased in 6 of the 7 patients studied. In Case 4 there was a 7 per cent in the present series and 23 per cent in the report of Dustan et al. are at variance with the lack of average change (−10 per cent) found by Aleksandrow and his co-workers. Similarly, the magnitude of change in averaged cardiac output was in agreement — −29 per cent for the present results and −23 per cent for those of Dustan and her associates (expressed as cardiac index) — but differed from those of Aleksandrow, Wysznacka and Gajewski[1] (−5 per cent). All 9 of the patients of Dustan and her coworkers exhibited decreased cardiac output after chlorothiazide; 6 of 7 of the present series showed a similar decrease, whereas only 2 of the 7 subjects studied by Aleksandrow et al. showed a decrease.

TABLE 2. *Comparison of Three Studies on Hemodynamic Effects of Chlorothiazide.*

STUDY GROUP	NO. OF CASES	CHANGE IN CARDIAC OUTPUT	CHANGE IN SYSTOLIC BLOOD PRESSURE	CHANGE IN DIASTOLIC BLOOD PRESSURE	CHANGE IN MEAN ARTERIAL PRESSURE	CHANGE IN TOTAL PERIPHERAL RESISTANCE	CHANGE IN PLASMA VOLUME
		%	%	%	%	%	%
Present series	7	−29	−17	−13	−15	+33	−13
Dustan et al.[2]	9	−23*	−11	−8	−6	+23	−14
Aleksandrow et al.[1]	7	−5	†	†	−19	−10	—

*Expressed as cardiac index.
†Value not given.

DISCUSSION

The present results are similar to those reported by Dustan et al.[2] They are, however, at some variance

The reduction of the pressure in the right atrium suggests that the fall in cardiac output was a conse-

quence of decreased filling pressures in the right side of the heart. The latter in turn may have been related to a decreased plasma volume, as reported by Freis et al.[7] and Tapia and his associates.[8] Although increased, the total peripheral resistance was not sufficiently elevated to maintain the level of the pretreatment basal blood pressure.

TABLE 1 *(Concluded).*

CASE NO.	TOTAL PERIPHERAL RESISTANCE		PLASMA VOLUME		BLOOD VOLUME		HEMATOCRIT		WEIGHT	
	CONTROL	EXPERIMENTAL*	CONTROL	EXPERIMENTAL*	CONTROL	EXPERIMENTAL*	CONTROL	EXPERIMENTAL*	CONTROL	EXPERIMENTAL*
	dynes cm.$^{-5}$ sec.	*dynes cm.$^{-5}$ sec.*	*ml.*	*ml.*	*ml.*	*ml.*	*mm.*	*mm.*	*kg.*	*kg.*
1†	1789	3486	2915	2760	4826	4936	39.5	41.1	76.4	76.4
2†	3314	3254	2379	1390	4102	2279	42.0	39.0	66.0	65.0
3†	1850	1425	—	—	—	—	48.0	48.8	95.5	88.6
4†	3243	5632	1951	1732	3101	2961	41.0	45.8	54.1	51.8
5†	1766	1795	3188	2946	4951	4709	38.1	38.0	90.0	82.7
6	1634	2500	3175	2526	6712	5526	52.7	53.0	85.9	83.6
7	1687	2283	2770	2968	4328	4566	36.0	35.0	78.6	77.7
Averages	2183	2911	2730	2387	4670	4163	42.5	43.0	78.2	75.0
Mean percentage change	+33		−13		−11		+1		−4	

*Results after 3 days of chlorothiazide therapy.
†Control value average of 3 separate determinations.

SUMMARY AND CONCLUSIONS

Cardiac output was determined in compensated hypertensive patients. Five were studied by the direct Fick method, and 2 by the dye-dilution technic before and after chlorothiazide therapy.

There was a reduction of cardiac output, mean arterial pressure, plasma and blood volumes, body weight and pressures in the right atrium. The total peripheral resistance was increased.

These data add support to the suggested mechanisms of the antihypertensive effect of chlorothiazide — namely, that contraction of plasma volume and possibly reduction of tissue pressure lead to a decrease in filling pressure in the right side of the heart and hence to a decreased cardiac output.

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